Meisenheimer rearrangements of *N*-allyl 2-azabornane derivatives

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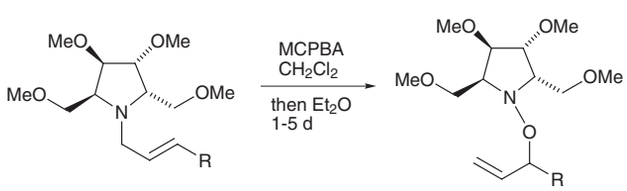
A study of the asymmetric [2,3]-Meisenheimer rearrangement of tertiary amine-*N*-oxides was carried out, in order to provide a method for the preparation of chiral allylic alcohols. The use of 2-azabornane as a chiral auxiliary gives rise to chiral tertiary amine-*N*-oxides, which undergo the [2,3]-Meisenheimer rearrangement with high levels of stereoselectivity. Reductive *N*,*O*-bond cleavage, mediated by ultrasound, of the *O*-allyl-hydroxylamine allows access to the chiral allylic alcohol.

Stereocontrolled transformations of allylic alcohols play an important role in modern organic synthesis. The diastereoselective functionalisation of chiral, secondary or tertiary allylic alcohols has received recent attention and methods to access enantiomerically-pure allylic alcohols are therefore of significance. One known approach to the allylic alcohol unit, including tertiary allylic alcohols, is the [2,3]-Meisenheimer rearrangement. The Meisenheimer rearrangement was first reported in 1919 and involves heating a tertiary amine-*N*-oxide to give a hydroxylamine product.[1] The extension of this rearrangement to allylic substrates *via* the [2,3]-sigmatropic process was reported by Cope and co-workers in the 1940s.[2]

Although the [2,3]-Meisenheimer rearrangement has been well documented in the literature,[3] only a handful of these reports address the stereospecific nature of this rearrangement. Of those that do, the most notable contributions have come from Inouye,[4] Reetz[5] and more recently Davies[6] and their co-workers, who have demonstrated that chirality is transferred across the allyl system in a 1,3 nature. However, only Enders and Kempen,[7] who obtained *O*-allyl-hydroxylamine products in 62–73% de, have investigated the extent of asymmetric induction in the presence of a chiral auxiliary (Scheme 1).



Scheme 1

The use of a C_2-symmetric auxiliary, as outlined in Scheme 1,[7] avoids the formation of a mixture of diastereomeric amine-*N*-oxides. A tertiary amine-*N*-oxide is configurationally stable and there exists the possibility of transferring chirality from the nitrogen to the carbon centre. The use of amines which were not C_2-symmetric in the report by Enders and Kempen[7] suggests that such asymmetric induction is very low. However, in these cases the diastereoselectivity on *N*-oxidation was unknown and it was therefore not possible to quantify the extent of any chirality transfer. Inouye and co-workers[8] have shown (Scheme 2) that a chiral tertiary amine-*N*-oxide of 16% ee gave rise, after [2,3]-Meisenheimer rearrangement, *N*,*O*-bond cleavage and olefin reduction, to a secondary alcohol with 13.6% ee. This result suggests that chirality transfer from the nitrogen atom to the carbon centre could be a useful procedure,

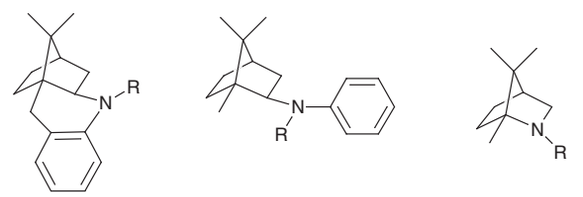
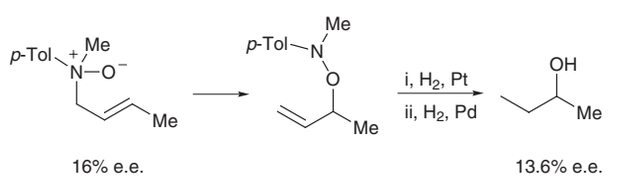


Fig. 1



Scheme 2

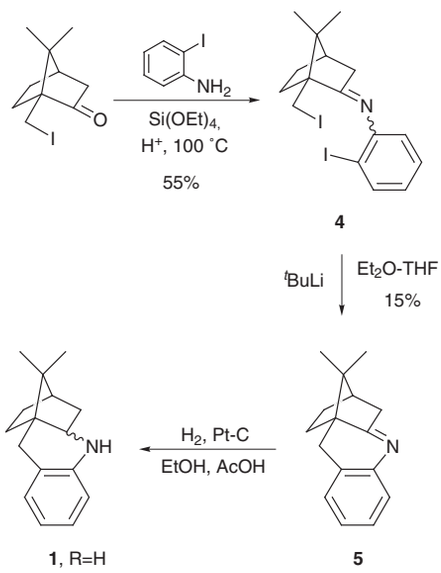
although in this case selectivity in the oxidation to the amine-*N*-oxide was low.

Our initial work in this area focused firstly on the use of chiral oxidants to achieve an enantioselective oxidation of the nitrogen atom; however although a wide range of oxidants were screened, none gave any enantioselectivity in the oxidation to the amine-*N*-oxide.[9] We then turned to investigate the use of chiral auxiliaries. We found that prolinol allowed a stereoselective oxidation but that the resulting amine-*N*-oxide was stabilised by the same hydrogen-bonding that allowed selectivity in the oxidation. This resulted in a reversible, non-stereospecific rearrangement.[9] We report in this paper the investigation of various chiral auxiliaries based on the camphor skeleton and the formation of allylic tertiary amine-*N*-oxides with high stereoselectivity and their rearrangement with transfer of chirality.[10]

There are many ways in which a nitrogen atom can be incorporated into a camphor-bearing chiral auxiliary. We have investigated a number of these, including those based on the structures **1**–**3**, in which the R group would become the required allylic group necessary to effect the [2,3]-Meisenheimer rearrangement (Fig. 1). We had reasoned that all of these auxiliaries would derive their selectivity by blocking the upper face of the molecule from oxidation, and thereby forming selectively the *endo* amine-*N*-oxide. Compounds **1** and **2** maintain the camphor skeleton, and have the nitrogen substituent at position 2. An aromatic amine, we believed, would prompt a more rapid rearrangement, despite being more

difficult to oxidise. In addition, these compounds should lead to a very well defined and rigid auxiliary which would hopefully promote a highly stereoselective oxidation and rearrangement. Auxiliary **2** (R = H) is a known compound.[11] Auxiliary **3**[12] has a disrupted camphor skeleton with a nitrogen atom within the bicyclic ring system. This auxiliary conforms to the principle of having the source of chiral induction as close as possible to the newly-forming chiral centre. A synthetic route was needed to prepare these compounds.

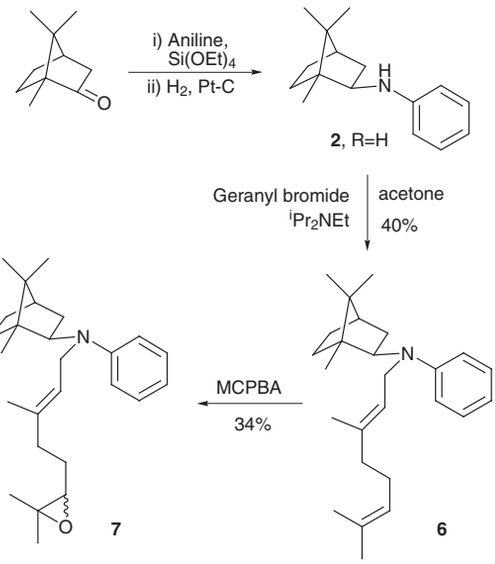
It was envisaged that the amine **1**, R = H could be synthesised from 10-iodocamphor[13] and a 2-haloaniline by means of imine formation and a ring closure. Successful imine formation was achieved using 2-iodoaniline and tetraethyl orthosilicate[14] as a dehydrating agent to give the imine **4** (Scheme 3). Many means



Scheme 3

were investigated to perform the subsequent ring closure, including treatment with a variety of palladium reagents, treatment with activated zinc followed by a palladium-catalysed closure or treatment with tributyltin hydride to attempt a radical-mediated closure. Whilst none of these methods was successful, a small amount of the desired cyclised imine **5** could be obtained by treating the imine **4** with one equivalent of *tert*-butyllithium. A preliminary attempt to reduce the imine **5** by catalytic hydrogenation gave what appeared to be the auxiliary **1**, R = H and its diastereomer (4:1), although this compound was not characterised fully. The yields in this synthesis were not sufficiently high to allow an investigation of this auxiliary in the Meisenheimer rearrangement. It is possible that one of the main reasons for the difficulties encountered in this synthesis lies with the geometry of the imine intermediate **4**, which probably prefers *E* stereochemistry, with the 2-iodophenyl substituent *trans* to the 10-iodo group. Attempted reduction of the imine **4** (which would allow free rotation about the C–N bond), prior to ring closure, led only to reduction of either or both of the iodine atoms in the molecule. An alternative approach, involving the formation of the carbon–carbon bond at the camphor 10-position before formation of the imine was unsuccessful using a variety of Heck, Stille or zinc-mediated palladium coupling conditions.[15]

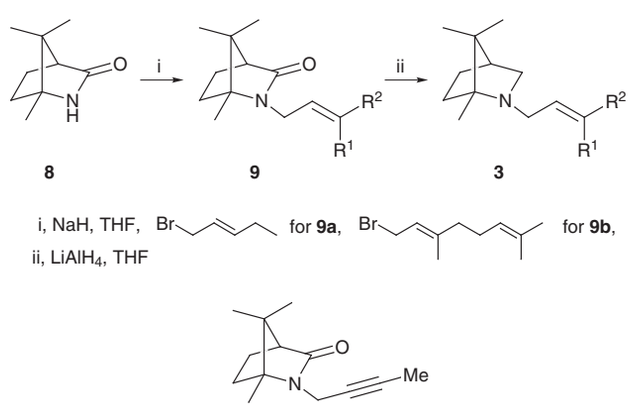
With the low yield in the formation of the auxiliary **1**, we turned our attention to the auxiliary **2**, R = H. This auxiliary was prepared easily by the reductive amination of camphor (Scheme 4).[11] Amine **2** was formed as a single diastereomer and could be alkylated in reasonable yield to give the amine **6**. Attempts to oxidise amine **6** to the desired *N*-oxide led only to the epoxide **7** as a mixture of diastereomers. Preferential epoxidation, rather than *N*-oxide formation, must be due to the



Scheme 4

difficulty in oxidising the less nucleophilic and more hindered nitrogen atom.

Having encountered these difficulties with the auxiliaries **1** and **2**, in which the nitrogen atom was located outside the camphor ring skeleton, we turned our attention to the 2-azabornane auxiliary **3**. We expected that placing the nitrogen atom closer to the chiral core of the camphor type structure would result in higher degrees of stereoselective oxidation to the amine-*N*-oxide. Therefore, by means of Boeckman *et al.*'s synthetic route[16] 2-azabicyclo[2.2.1]heptan-3-one **8** was prepared. This could be *N*-allylated (Scheme 5) to give the lactam **9a**

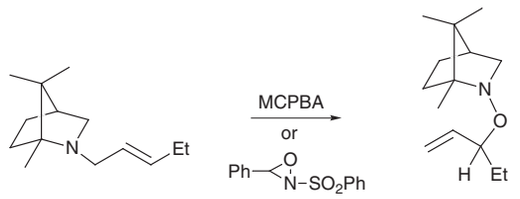


Scheme 5

(R^1 = H, R^2 = Et, 96%), formed as a mixture of geometrical isomers (*E*:*Z*, 6:1). When alkylation was performed with geranyl bromide, the lactam **9b** (R^1 = Me, R^2 = CH_2CH_2-CH=CMe_2, 94%) was formed (*E* isomer only), together with a small amount of the *O*-alkylated product (5:1). The lactams **9** could be reduced by refluxing in THF with a large excess of $LiAlH_4$ to the amines **3a** (76%) and **3b** (87%). Both geometrical isomers of the *N*-but-2-enyl derivative of amine **3** could be obtained from lactam **10**; the *E*-amine **3c**, R^1 = H, R^2 = Me (*E*:*Z*, 6:1) by successive reduction of the lactam **10** with $LiAlH_4$ followed by DIBAL-H (overall 36%), and the *Z*-amine **3d**, R^1 = Me, R^2 = H (*E*:*Z*, 1:6) by hydrogenation with the Lindlar catalyst, followed by reduction of the lactam with $LiAlH_4$ (overall 46%).

The oxidation–rearrangement of the amine **3a** was investigated under a range of conditions that we had found previously to be successful[9] (Table 1). The results show that the yields and

Table 1 Oxidation and rearrangement of the amine **3a**

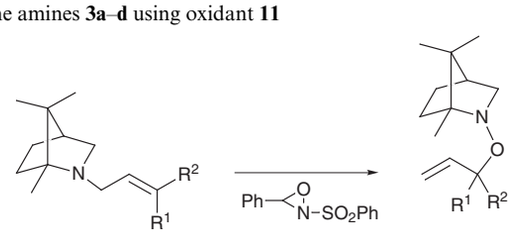


3a **11** **12a**

N-Oxidation				Rearrangement					
		Conditions			Conditions				
Oxidant	Solvent	*T*/°C	*t*/h	Solvent	*T*/°C	*t*/h	Yield (%)	de (%)	de (%)[a]
MCPBA	CH_2Cl_2	0	1	THF	60	15	80	40	56
MCPBA	CH_2Cl_2	−78	1	THF	60	16	40	40	56
MCPBA	CH_2Cl_2	−78	1	Et_2O	35	15	40	40	56
MCPBA	CH_2Cl_2	−78	1	Acetone	60	18	68	42	59
MCPBA	CH_2Cl_2	−78	1	Hexane	60	18	78	42	59
MCPBA	CH_2Cl_2	−78	1	MeCN	60	18	68	43	60
MCPBA	CH_2Cl_2	−78	1	MeOH	60	18	55	36	50
MCPBA	CH_2Cl_2	−78	1	CH_2Cl_2	40	18	59	40	56
MCPBA	Toluene	−78	1	THF	60	15	68	38	53
MCPBA	Et_2O	−78	4	Et_2O	20	20	29	50	70
11	CH_2Cl_2	20	40	THF	60	15	59	44	62
11	Et_2O	20	24	Et_2O	20	24	48	61	86

[a] Diastereoselectivity taking *E*:*Z* ratio into account.

Table 2 Oxidation and rearrangement of the amines **3a**–**d** using oxidant **11**



3 **11** **12**

Amine	R^1	R^2	Conditions	Product	Yield (%)	de (%)	de (%)[a]
3a	H	Et	Et_2O, rt	**12a**	48	61	86
3b	Me	$CH_2CH_2CH{=}CMe_2$	Et_2O, rt	**12b**	25	65	65
3c	H	Me	Et_2O, rt	**12c**	19	67	94
3d	Me	H	Et_2O, rt	**12d**	19	36[b]	50

[a] Diastereoselectivity taking *E*:*Z* ratio into account. [b] Diastereoselectivity opposite to **12c**.

diastereoselectivities are broadly independent of the solvent used for the rearrangement, once the by-product from MCPBA had been extracted with a basic solution. Subsequent observation suggested that the rearrangement occurs rapidly once the CH_2Cl_2 solution had been washed with base, and therefore the change of solvent was unnecessary. By using the oxidant in diethyl ether and allowing *in situ* rearrangement, the diastereoselectivity was enhanced, although at the expense of a slightly lower yield of isolated hydroxylamine product **12**. Further experiments with other oxidants showed that the best conditions for this oxidation–rearrangement process involve the use of the Davis sulfonyl oxaziridine[17] **11** in ether, which gave a reasonable yield together with a high level of diastereoselectivity.

Each of the *N*-allyl-2-azabornanes **3** were treated using the optimised oxidation–rearrangement conditions with the Davis oxaziridine reagent **11**;[17] these results are shown in Table 2. The hydroxylamines **12a**–**c** were formed with diastereomeric excesses of 61–67% (determined by NMR and/or HPLC), which are among the best recorded for the Meisenheimer rearrangement.[7] The *Z*-isomer **3d** underwent the oxidation and rearrangement process in a less selective manner. Since the amines **3a**, **3c** and **3d** are mixtures of geometrical isomers in a ratio of 6:1, a stereospecific rearrangement would give a maximum selectivity of 71% de. Assuming that the minor geometrical isomer of the amine **3** rearranges to give the minor diastereomer of the hydroxylamine **12**, then the oxidation and rearrangement of the major geometrical isomer of the amine **3** occur with up to 94% de. Since it was not possible to isolate any of the intermediate amine-*N*-oxides (and determine their diastereomeric ratio), the lack of complete stereochemical control could arise from either the oxidation or the rearrangement step (or both).

Since a knowledge of the level of selectivity upon oxidation of the amines **3** is critical to understanding the selectivity of the combined oxidation–rearrangement process, the oxidation of *N*-benzyl-2-azabornane **13** was investigated. This could be prepared easily by an analogous route to the amines **3**. Oxidation with MCPBA in CH_2Cl_2, followed by washing with aqueous potassium carbonate solution led to the isolation of the Cope elimination[18] product **15**. Analysis by NMR showed that the amine-*N*-oxide was present initially but fragmented fairly

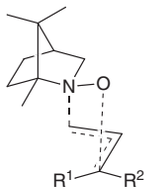
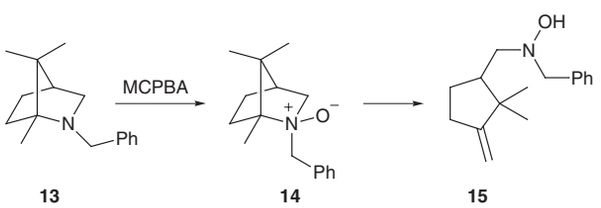


Fig. 2

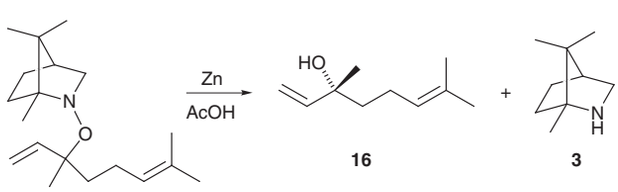
rapidly ($t_{1/2}$ 1 h). However, by performing the oxidation in deuteriochloroform (without removing the acidic oxidant–by-product), complete conversion to the amine-*N*-oxide was seen by NMR. This amine-*N*-oxide was stable under these conditions, presumably as the carboxylic acid complexes to the *N*-oxide. Both diastereomers of the amine-*N*-oxide were observed in a ratio of 6:1, with NOESY experiments demonstrating that the major diastereomer was the *exo*-*N*-oxide **14**, as illustrated (Scheme 6). This suggests that the oxidant preferentially approaches from an *exo* orientation with the *N*-substituent in the *endo* conformation. This is consistent with theoretical studies on the conformation of *N*-methyl-2-azabicyclo[2.2.1]heptane.[19] Thus it seems reasonable to expect that the *N*-allyl-2-azabornanes **3** would also undergo oxidation preferentially from the *exo*-face. The subsequent [2,3]-Meisenheimer rearrangement is therefore faster than the competing Cope elimination.



13 **14** **15**

Scheme 6

The absolute configuration of the *O*-allyl-hydroxylamine **12b** was deduced by cleaving the N–O bond, with zinc and acetic acid under ultrasound conditions, in order to give linalool[20] **16** (45%) and the recovered 2-azabornane auxiliary **3**, R = H (45%) (Scheme 7). Hydroxylamine **12b** (46% de) gave linalool (46% ee), as determined by chiral GC. This demonstrates that the N–O cleavage process does not affect the stereochemical integrity. The product linalool was found to be in favour of the *R*-isomer. It seems likely that the [2,3]-sigmatropic rearrangement proceeds *via* a five-membered ring transition state, such as that depicted in Fig. 2.



12b **16** **3**

Scheme 7

Conclusion

A range of nitrogen-containing camphor-derived chiral auxiliaries have been designed for the Meisenheimer rearrangement of allylic amine-*N*-oxides. The most promising of these was that based on the 2-azabornane ring system. A selection of allylic amines bearing the 2-azabornane auxiliary was oxidised successfully and rearranged to give some of the highest diastereoselectivities for this process yet seen in the Meisenheimer rearrangement. It was demonstrated that the rearrangement is rapid and proceeds with very high stereoselectivity. The product hydroxylamine can be converted to the corresponding allylic alcohol with no loss in enantioselectivity.

Experimental

General

Optical rotations were measured on an Optical Activity Ltd. AA-1000 polarimeter, using a cell with a path length of 0.5 dm and are given in units of 10^{-1} deg cm^2 g^{-1}. IR spectra were recorded as liquid films on NaCl plates unless otherwise stated, using a Perkin Elmer 881 spectrometer. ^{1}H NMR spectra were recorded on a Bruker AM 250 MHz, JEOL GX 270 MHz, Bruker AC 300 MHz, Bruker AMX 400 MHz or Bruker Avance DPX 400 MHz spectrometer using the solvent ($CDCl_3$) as an internal lock. Chemical shifts are given in parts per million. Coupling constants, *J*, are given in Hz. ^{13}C NMR spectra are recorded on the above spectrometers operating at 63, 68, 75 or 100 MHz respectively and are proton decoupled. Additional analysis by DEPT, HMQC and HMBC experiments was performed where necessary. Mass spectra were measured on either a Kratos Profile HV3 spectrometer using electron impact ionisation, or a VG Trio-2 single quadrapole spectrometer, with electron impact or ammonium ion ionisation.

THF was freshly distilled from the sodium benzophenone ketal. Petrol refers to light petroleum (bp 40–60 °C). Petrol, CH_2Cl_2 and ethyl acetate (EtOAc) were all distilled before use. Flash column chromatography was performed on silica gel 60H (230–400 mesh) (Merck 9385). TLC was performed on Kieselgel $60F_{254}$ 0.25 mm plates, and visualised by UV irradiation at 254 nm or with a potassium permanganate dip. Ultrasonic irradiation was achieved by immersion in a Sonicor SC-120 cleaning bath. Hydrogenation was performed at 1 atmosphere.

MCPBA (35% supplied by Jannsen) was concentrated to ~85% before use by washing with a phosphate buffer solution at pH 7.5. Zinc dust was activated by sequential washing in hydrochloric acid (2 M), water and ethanol, followed by drying *in vacuo*. *exo*-Bornyl aniline,[11] 2-azabicyclo[2.2.1]heptan-3-one **8**[16] and the (±)-Davis oxaziridine **15**[17] were prepared according to literature methods. Other chemicals were used as supplied.

2-Iodo-*N*-(10-iodobornan-2-ylidene)aniline 4

To a solution of (1*S*)-(+)-camphorsulfonic acid (4.64 g, 20 mmol) in toluene (150 cm^3) was added iodine (10.1 g, 40 mmol) and triphenylphosphine (26.2 g, 100 mmol). The solution was heated at reflux for 16 h. The toluene was removed *in vacuo*, and EtOAc (200 cm^3) was added. The mixture was washed with saturated sodium thiosulfate solution (3 × 30 cm^3), H_2O (10 cm^3) and brine (10 cm^3) and dried (Na_2SO_4). The solvent was removed *in vacuo* and the residue was purified by dry flash column chromatography, eluting with a gradient of EtOAc in petrol, followed by flash chromatography, eluting with petrol–acetone (9:1), to give 10-iodocamphor[13] (5.1 g, 92%) as needles, mp 70–72 °C (lit.[13] 71 °C); $[\alpha]_D^{22}$ −21.2 (*c* 1.0 in $CHCl_3$); δ_H(300 MHz, $CDCl_3$) 0.89 (3H, s, CH_3), 1.06 (3H, s, CH_3), 1.38 (1H, t, *J* 9, 5-H$_{endo}$), 1.59 (1H, t, *J* 9, 6-H$_{endo}$), 1.89 (1H, d, *J* 18, 3–H$_{endo}$), 1.93–2.02 (2H, m, 5-H$_{exo}$ and 6-H$_{exo}$), 2.13–2.16 (1H, m, 4-H), 2.38 (1H, ddd, *J* 18, 5 and 2, 3-H$_{exo}$), 3.10 (1H, d, *J* 11, 10-*H*^{A}H^B), 3.30 (1H, d, *J* 11, 10-H^A*H*^{B}).

10-Iodocamphor (278 mg, 1 mmol), 2-iodoaniline (328 mg, 1.5 mmol), tetraethyl orthosilicate (0.335 cm^3, 1.5 mmol) and concentrated sulfuric acid (1 drop) were heated in the absence of solvent at 100 °C for 16 h, distilling ethanol as it was formed. The mixture was extracted with EtOAc (3 × 10 cm^3), washed with NaOH (4 M, 2 × 10 cm^3), H_2O (10 cm^3) and brine (5 cm^3) and dried (Na_2SO_4). The solvent was removed *in vacuo* and the residue was purified by flash chromatography, eluting with

petrol–Et_2O (9:1), to give the imine **4** (454 mg, 95%) as orange needles, mp 69–73 °C; R_f 0.64 (9:1, petrol–EtOAc); $[\alpha]_D^{24}$ +18.6 (*c* 1.0 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 1685 (C=N); δ_H(400 MHz, $CDCl_3$) 0.99 (3H, m, CH_3), 1.12 (3H, m, CH_3), 1.30–1.36 (1H, m, 5-H_{endo}), 1.73 (1H, d, *J* 17, 3-H_{endo}), 1.83–1.99 (3H, m, 5-H_{exo}, 6-H_{endo} and 6-H_{exo}), 2.08–2.17 (2H, m, 3-H_{exo} and 4-H), 3.39 (1H, d, *J* 10, 10-CH^AH^B), 3.66 (1H, d, *J* 10, 10-CH^AH^B), 6.66 (1H, dd, *J* 8 and 2, Ar*H*), 6.75 (1H, td, *J* 8 and 2, Ar*H*), 7.25 (1H, td, *J* 8 and 2, Ar*H*), 7.75 (1H, dd, *J* 8 and 2, Ar*H*); δ_C(100 MHz, $CDCl_3$) 3.57 (10-CH_2I), 18.12 (CH_3), 20.27 (CH_3), 26.98 (5-C), 32.28 (6-C), 36.41 (3-C), 45.24 (4-C), 49.07 (7-C), 55.37 (1-C), 89.26 (Ar*C*I), 118.99 (Ar*C*H), 124.87 (Ar*C*H), 128.96 (Ar*C*H), 139.05 (Ar*C*H), 152.44 (Ar*C*N), 182.34 (C=N) (Found: M^+ 478.9626. $C_{16}H_{19}NI_2$ requires M, 478.9607); *m*/*z* 479 (8%, M^+), 352 (100, M − I), 224 (19, M − I_2).

Imine 5

tert-Butyllithium (0.9 M in pentane, 0.35 cm^3, 0.30 mmol) was added to the diiodide **4** (129 mg, 0.27 mmol) in dry Et_2O (5 cm^3) at −90 °C under argon. The mixture was allowed to warm to room temperature and was stirred for 16 h before being quenched with saturated NH_4Cl solution. The mixture was extracted with Et_2O (3 × 5 cm^3), washed with H_2O (5 cm^3) and brine (5 cm^3) and dried (Na_2SO_4). The solvent was removed *in vacuo* and the residue was purified by flash chromatography, eluting with petrol–EtOAc (3:1), to give the imine **5** (9 mg, 0.04 mmol, 15%) as an oil; R_f 0.21 (3:1, petrol–EtOAc); $[\alpha]_D^{24}$ −92.5 (*c* 1.2 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 1660 (C=N); δ_H(400 MHz, $CDCl_3$) 0.96 (3H, s, CH_3), 1.01 (3H, s, CH_3), 1.28–1.36 (1H, m, 5-H_{endo}), 1.51–1.64 (2H, m, 6-H_{endo} and 6-H_{exo}), 1.90–1.99 (1H, m, 5-H_{exo}), 2.05 (1H, t, *J* 5, 4-H), 2.16 (1H, d, *J* 18, 3-H_{endo}), 2.60 (1H, d, *J* 17, 10-H^AH^B), 2.78 (1H, dt, *J* 18 and 4, 3-H_{exo}), 2.90 (1H, d, *J* 17, 10-H^AH^B), 7.07–7.15 (2H, m, Ar*H*), 7.19–7.23 (1H, m, Ar*H*), 7.29–7.31 (1H, m, Ar*H*); δ_C(100 MHz, $CDCl_3$) 18.44 (CH_3), 20.97 (CH_3), 26.42 (10-C), 26.93 (5-C), 30.93 (6-C), 40.03 (3-C), 43.23 (4-C), 48.01 (7-C), 50.93 (1-C), 124.63 (Ar*C*), 126.54 (Ar*C*H), 126.56 (Ar*C*H), 127.19 (Ar*C*H), 128.96 (Ar*C*H), 143.52 (Ar*C*N), 183.14 (*C*=N) (Found: M^+ 225.1523. $C_{16}H_{19}N$ requires *M*, 225.1518); *m*/*z* 225 (87%, M^+), 210 (22, M − Me), 182 (100, M − H − CMe_2).

N-Geranyl-*N*-phenyl-2-*exo*-bornylamine 6

To a solution of the amine **2** (R = H)[11] (110 mg, 0.48 mmol) in acetone (15 cm^3) was added Hünig's base (132 μl, 0.76 mmol) and geranyl bromide (142 μl, 0.72 mmol) and the mixture was heated under reflux for 16 h. The solvent was removed *in vacuo*, the residue was extracted with EtOAc (2 × 10 cm^3), washed with H_2O (3 × 5 cm^3), brine (5 cm^3) and was dried (Na_2SO_4). The residue was purified by flash chromatography, eluting with petrol–CH_2Cl_2 (19:1), to give the amine **6** (71 mg, 40%) as an oil; R_f 0.51 (petrol–CH_2Cl_2, 9:1); $[\alpha]_D^{26}$ +42.7 (*c* 0.75 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 1595 and 1500 (Ar); δ_H(400 MHz, $CDCl_3$) 0.83 (3H, s, CH_3), 0.85 (3H, s, CH_3), 0.98 (3H, s, CH_3), 1.12–1.21 (1H, m, 5-H_{endo}), 1.27–1.34 (1H, m, 3-H_{endo}), 1.45 (3H, s, CH_3), 1.49–1.58 (2H, m, 3-H_{exo} and 5-H_{exo}), 1.59 (3H, s, CH_3), 1.64 (1H, t, *J* 4, 4-H), 1.68 (3H, d, *J* 2, NCH_2CH=CCH_3), 1.69–1.77 (2H, m, 6-CH_2), 1.89–1.96 (2H, m, CH_2CH_2CH=CMe_2), 1.99–2.05 (2H, m, CH_2CH=CMe_2), 3.46 (1H, dd, *J* 9 and 7, 2-H_{endo}), 3.73 (2H, d, *J* 5, NCH_2CH), 5.05 (1H, tt, *J* 7 and 1, C*H*=CMe_2), 5.09–5.15 (1H, m, NCH_2CH), 6.89 (1H, td, *J* 7 and 2, Ar*H*), 6.94 (2H, d, *J* 7, Ar*H*), 7.22 (2H, td, *J* 7 and 2, Ar*H*); δ_C(100 MHz, $CDCl_3$) 13.44 (10-CH_3), 16.02 (CH_3), 17.67 (CH_3), 20.36 (CH_3), 21.22 (CH_3), 25.68 (CH_3), 26.41 (5-C), 27.26 (CH_2CH=CMe_2), 36.56 (6-C), 36.83 (3-C), 39.53 (CH_2CH_2CH=CMe_2), 44.85 (4-C), 46.94 (7-C), 50.25 (NCH_2), 50.28 (1-C), 67.45 (2-C), 120.36 (Ar*C*H), 122.13 (Ar*C*H), 122.98 (NCH_2CH=), 124.29 (*C*H=CMe_2), 128.27 (Ar*C*H), 131.25 (CH=*C*Me_2), 136.21 (NCH_2CH=*C*), 151.63 (Ar*C*N) (Found: M^+ 365.3073. $C_{26}H_{39}N$ requires *M*, 365.3086); *m*/*z* 365 (15%, M^+), 296 (53, M − C_5H_9), 229 (18, M − $C_{10}H_{17}$), 77 (54, Ph), 69 (100, C_5H_9).

N-(6,7-Epoxygeranyl)-*N*-phenyl-2-*exo*-bornylamine 7

To a solution of the amine **6** (128 mg, 0.35 mmol) in CH_2Cl_2 (5 cm^3) was added MCPBA (76 mg, 0.35 mmol) at room temperature. After 16 h the solvent was removed *in vacuo* and the residue was purified by flash chromatography, eluting with petrol–Et_2O (19:1), to give the epoxide **7** (45 mg, 34%) as an oil (as a 1:1 mixture of diastereomers); $[\alpha]_D^{25}$ +26.8 (*c* 0.5 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 1595 (Ar); δ_H(400 MHz, $CDCl_3$) 0.81 (3H, s, CH_3), 0.84 (3H, s, CH_3), 0.96 (3H, s, CH_3), 1.10–1.20 (2H, m, 5-H_{endo} and 6-H_{endo}), 1.24 (3H, s, CH_3), 1.26–1.29 (5H, m, CH_3, 3-H_{endo} and 6-H_{exo}), 1.45 (3H, s, CH_3), 1.47–1.77 (5H, m, OCHCH_2, 3-H_{exo}, 4-H, 5-H_{exo}), 2.00–2.10 (2H, m, NCH_2CH=$CMeCH_2$), 2.63 (0.5H, dd, *J* 6 and 2, Me_2CCH^A), 2.64 (0.5H, dd, *J* 6 and 2, Me_2CCH^B), 3.42 (1H, t, *J* 7, 2-H), 3.71 (2H, br s, NCH_2CH), 5.15 (1H, br s, NCH_2CH), 6.89–6.93 (3H, m, Ar*H*), 7.20 (2H, t, *J* 8, Ar*H*); δ_C(100 MHz, $CDCl_3$) 13.50 (CH_3), 16.03 and 16.04 (CH_3), 18.68 (CH_3), 20.30 (CH_3), 21.16 (CH_3), 24.85 (CH_3), 27.24 and 27.30 (5-C), 36.18 (CH_2), 36.63 (CH_2), 36.66 (CH_2), 36.82 (CH_2), 44.83 (4-C), 46.94 (7-C), 50.22 (1-C), 50.72 and 50.77 (NCH_2), 58.24 and 58.26 (Me_2CO), 63.93 and 63.98 (2-C), 67.68 and 67.73 (Me_2CCO), 120.76 and 120.80 (Ar*C*H), 122.63 and 122.70 (Ar*C*H), 123.46 and 123.50 (NCH_2CH), 128.29 (Ar*C*H), 135.44 and 135.47 (NCH_2CH=*C*), 151.53 and 151.55 (Ar*C*N) (Found: M^+ 381.3025. $C_{26}H_{39}NO$ requires *M*, 381.3032); *m*/*z* 381 (58%, M^+), 95 (100), 77 (83, Ph).

1,7,7-Trimethyl-2-(pent-2-enyl)-2-azabicyclo[2.2.1]heptan-3-one 9a

To a solution of 2-azabornan-3-one **8**[16] (765 mg, 5 mmol) in THF (30 cm^3) was added NaH (60% dispersion in mineral oil, 800 mg, 20 mmol). After 1 h, pent-2-enyl bromide (0.95 cm^3, 8 mmol) was added. After a further 16 h, saturated NH_4Cl solution was added dropwise. The mixture was extracted with Et_2O (3 × 10 cm^3), washed with H_2O (2 × 10 cm^3) and brine (10 cm^3) and dried (Na_2SO_4). The solvent was removed *in vacuo* and the residue was purified by flash chromatography, eluting with Et_2O, to give the lactam **9a** (1.06 g, 96%) as an oil (*E*:*Z*, 6:1 by NMR); R_f 0.50 (Et_2O); $[\alpha]_D^{24}$ +0.8 (*c* 1.5 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 1695s (C=O); δ_H(400 MHz, $CDCl_3$) (*E* isomer only) 0.82 (3H, s, CH_3), 0.91 (3H, t, *J* 4, CH_2CH_3), 0.95 (3H, s, CH_3), 1.26 (3H, s, 10-CH_3), 1.40–1.47 (1H, m, 5-H_{endo}), 1.51–1.58 (1H, m, 6-H_{endo}), 1.71 (1H, ddd, *J* 12, 10 and 4, 6-H_{exo}), 1.85–1.93 (1H, m, 5-H_{exo}), 1.93–2.01 (2H, m, CH_2CH_3), 2.24 (1H, d, *J* 4, 4-H), 3.65 (1H, ddd, *J* 15, 6 and 1, NCH^AH^B), 3.74 (1H, ddd, *J* 15, 6 and 1, NCH^AH^B), 5.29–5.37 (1H, m, NCH_2CH), 5.56–5.64 (1H, m, NCH_2CH=C*H*); δ_C(100 MHz, $CDCl_3$) 12.04 and 12.16 (10-CH_3, *Z* and *E*), 13.34 and 13.94 (CH_2CH_3, *E* and *Z*), 18.06 (CH_3), 18.41 (CH_3), 23.47 (5-C), 20.56 and 25.13 (CH_2CH_3, *Z* and *E*), 33.70 and 33.73 (6-C, *E* and *Z*), 35.38 and 40.54 (NCH_2, *Z* and *E*), 49.78 and 49.83 (7-C, *E* and *Z*), 55.10 and 55.12 (4-C, *E* and *Z*), 70.52 and 70.67 (1-C, *Z* and *E*), 125.07 and 125.15 (NCH_2CH, *E* and *Z*), 133.63 and 134.91 (NCH_2-CH=*C*H, *Z* and *E*), 177.64 (3-C=O) (Found: M^+ 221.1784. $C_{14}H_{23}NO$ requires *M*, 221.1780); *m*/*z* 221 (75%, M^+), 193 (84, MH − Et), 178 (100), 110 (96, M − CON − C_5H_9), 69 (89, C_5H_9).

1,7,7-Trimethyl-2-(pent-2-enyl)-2-azabicyclo[2.2.1]heptane 3a

To a suspension of $LiAlH_4$ (616 mg, 16.2 mmol) in THF (25 cm^3) at 0 °C was added the lactam **9a** (717 mg, 3.24 mmol) in THF (10 cm^3). The mixture was heated under reflux for 24 h, before being quenched by the dropwise addition of NaOH (4 M). EtOAc (30 cm^3) and Na_2SO_4 were added and the mixture was filtered, evaporated and purified by flash chromatography, eluting with Et_2O–MeOH (9:1), to give the amine **3a** (586 mg,

87%) as an oil (*E*:*Z*, 6:1 by NMR); $[\alpha]_D^{24}$ +79.2 (*c* 1.5 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 2950 (C–H); δ_H(400 MHz, $CDCl_3$) (*E* isomer only) 0.90 (3H, s, CH_3), 0.91 (3H, s, CH_3), 0.98 (3H, t, *J* 8, CH_2CH_3), 1.04 (3H, s, 10-CH_3), 1.10–1.17 (1H, m, 5-H_{endo}), 1.38–1.45 (1H, m, 6-H_{endo}), 1.59 (1H, t, *J* 4, 4-H), 1.64–1.73 (1H, m, 5-H_{exo}), 1.80–1.87 (1H, m, 6-H_{exo}), 1.86 (1H, d, *J* 9, 3-H_{endo}), 1.98–2.06 (2H, m, CH_2CH_3), 2.78 (1H, dd, *J* 13 and 7, NCH^AH^BCH=), 3.18–3.24 (2H, m, 3-H_{exo} and NCH^AH^BCH=), 5.39–5.47 (1H, m, NCH_2CH=), 5.56–5.64 (1H, m, $CHCH_2CH_3$); δ_C(100 MHz, $CDCl_3$) 13.75 (CH_2CH_3), 14.04 (10-CH_3), 18.41 and 18.46 (8-CH_3, *Z* and *E*), 19.84 (9-CH_3), 25.38 (CH_2), 27.81 and 27.97 (6-C, *Z* and *E*), 28.40 and 28.49 (5-C, *E* and *Z*), 45.18 and 45.21 (4-C, *E* and *Z*), 45.68 and 51.45 (NCH_2CH, *Z* and *E*), 47.66 (7-C), 58.42 and 58.47 (3-C, *E* and *Z*), 66.83 (1-C), 128.38 and 128.42 ($CHCH_2CH_3$, *Z* and *E*), 132.16 and 132.55 (NCH_2CH=, *Z* and *E*) (Found: M^+ 207.1997. $C_{14}H_{25}N$ requires *M*, 207.1987); *m*/*z* 207 (1%, M^+), 152 (43, M − C_4H_7), 69 (77, C_5H_9), 55 (100, C_4H_7).

1,7,7-Trimethyl-2-(pent-1-en-3-yloxy)-2-azabicyclo[2.2.1]-heptane 12a

The oxaziridine (±)-**11**[17] (0.38 mmol, 98 mg) was added to the amine **3a** (52 mg, 0.25 mmol) in Et_2O (4 cm^3) at room temperature. After 48 h, the solvent was removed *in vacuo* and the residue was purified by flash chromatography, eluting with petrol–Et_2O (9:1), to give the hydroxylamine **12a** (27 mg, 48%) as an oil (61% de by ^1H NMR); ν_{max}(neat)/cm^{-1} 2960 (C–H), 1645 (C=C); δ_H(400 MHz, $CDCl_3$) 0.84–0.93 (6H, m, CH_2CH_3 and CH_3), 0.96–1.01 (6H, m, 2 × CH_3), 1.29–1.36 (1H, br m, 6-H_{endo}), 1.40–1.75 (5H, m, CH_2CH_3, 4-H, 5-H_{endo} and 5-H_{exo}), 2.30 (1H, br s, 6-H_{exo}), 2.50 (1H, br s, 3-H_{endo}), 3.49 (1H, br s, 3-H_{exo}), 3.76–3.89 (1H, m, OCH), 5.05–5.18 (2H, m, $CH=CH_2$), 5.69–5.80 (1H, m, $CH=CH_2$); δ_C(100 MHz, $CDCl_3$) (major diastereomer first) 9.30 and 10.23 (CH_2CH_3), 13.93 (CH_3), 18.66 (CH_3), 20.25 and 20.15 (CH_3), 26.16 (CH_2CH_3), 26.82 (5-C), 27.82 (6-C), 45.25 (4-C), 46.41 and 46.37 (7-C), 61.33 and 61.62 (3-C), 70.86 (1-C), 85.26 and 86.37 (OCH), 115.32 and 115.45 ($CH=CH_2$), 139.05 and 141.02 ($CH=CH_2$) (Found: M^+ 223.1929. $C_{14}H_{25}NO$ requires *M*, 223.1936); *m*/*z* 223 (10%, M^+), 155 (69, MH − C_5H_9), 154 (95, M − C_5H_9), 109 (100) and 69 (41, C_5H_9).

2-Geranyl-1,7,7-trimethyl-2-azabicyclo[2.2.1]heptan-3-one 9b

Following the same procedure as for the lactam **9a**, the lactam **8** (918 mg, 6 mmol), NaH (60% dispersion in mineral oil, 960 mg, 24 mmol) and geranyl bromide (1.78 cm^3, 9 mmol) gave, after purification by flash chromatography, eluting with Et_2O–EtOAc (9:1), the lactam **9b** and 3-geranyloxy-2-azabornane (1.64 g, 94%, 5:1). Further flash chromatography provided the lactam **9b**; $[\alpha]_D^{22}$ +0.3 (*c* 1.5 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 1695 (C=O); δ_H(400 MHz, $CDCl_3$) 0.85 (3H, s, 9-CH_3), 0.93 (3H, s, 8-CH_3), 1.13 (3H, s, 10-CH_3), 1.42–1.50 (1H, m, 5-H_{endo}), 1.55–1.62 (1H, m, 6-H_{endo}), 1.57 (3H, s, CH_3), 1.65 (3H, d, *J* 1, $NCH_2CH=CCH_3$), 1.66 (3H, s, CH_3), 1.68–1.76 (1H, m, 6-H_{exo}), 1.88–1.94 (1H, m, 5-H_{exo}), 1.94–2.01 (2H, m, CH_2CH_2CH=), 2.03–2.09 (2H, m, CH_2CH_2CH=), 2.26 (1H, d, *J* 4, 4-H), 3.75–3.80 (2H, m, NCH_2CH), 5.01–5.06 (1H, m, $CH=CMe_2$), 5.06–5.11 (1H, m, NCH_2CH=); δ_C(100 MHz, $CDCl_3$) 12.00 (10-C), 16.08 (CH_3), 17.64 (CH_3), 18.08 (8-C), 18.39 (9-C), 23.50 (5-C), 25.66 ($CH=CCH_3$), 26.18 (CH_2CH_2CH=), 33.76 (6-C), 36.31 (NCH_2), 39.43 (CH_2CH_2CH=), 49.86 (7-C), 55.22 (4-C), 70.39 (1-C), 120.78 (NCH_2CH), 124.01 ($CH=CMe_2$), 131.51 ($CH=CMe_2$), 137.51 ($NCH_2CH=C$), 177.42 (C=O) (Found: M^+ 289.2413. $C_{19}H_{31}NO$ requires *M*, 289.2405); *m*/*z* 289 (17%, M^+), 166 (38), 85 (90), 83 (100, C_6H_{11}), 69 (58, C_5H_9).

2-Geranyl-1,7,7-trimethyl-2-azabicyclo[2.2.1]heptane 3b

Following the same procedure as for the amine **3a**, $LiAlH_4$ (230 mg, 6 mmol) and the lactam **9b** (1.15 g, 4 mmol) gave, after purification by flash chromatography, eluting with Et_2O–MeOH (9:1), the amine **3b** (837 mg, 76%) as an oil; $[\alpha]_D^{24}$ +59.1 (*c* 1.6 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 2950s (C–H); δ_H(400 MHz, $CDCl_3$) 0.90 (3H, s, 9-CH_3), 0.93 (3H, s, 8-CH_3), 1.04 (3H, s, 10-CH_3), 1.11–1.19 (1H, m, 6-H_{endo}), 1.38–1.46 (1H, m, 5-H_{endo}), 1.58–1.61 (1H, m, 4-H), 1.60 (3H, s, $C=CMe^AMe^B$), 1.64 (3H, s, $C=CCH_3$), 1.68 (3H, d, *J* 1, $C=CMe^AMe^B$), 1.69–1.74 (1H, m, 6-H_{exo}), 1.86 (1H, d, *J* 9, 3-H_{endo}), 1.87–1.94 (1H, m, 5-H_{exo}), 1.96–2.03 (2H, m, $CH=CMe\text{-}CH_2$), 2.05–2.12 (2H, m, $CH_2\text{-}CH=CMe_2$), 2.98 (1H, dd, *J* 13 and 7, NCH^AH^BCH=), 3.12 (1H, dd, *J* 13 and 5, NCH^AH^BCH=), 3.24 (1H, dt, *J* 9 and 4, 3-H_{exo}), 5.10 (1H, tt, *J* 7 and 1, $CH=CMe_2$), 5.20–5.24 (1H, m, NCH_2CH=); δ_C(100 MHz, $CDCl_3$) 14.06 (8-C), 14.40 ($NCH_2\text{-}CH=CMe$), 17.66 ($CH=CMe^AMe^B$), 18.47 (10-C), 19.88 (9-C), 25.69 ($CH=CMe^AMe^B$), 26.59 ($CH_2CH=CMe_2$), 27.75 (5-C), 28.48 (6-C), 39.79 ($CMeCH_2CH_2$), 45.17 (4-C), 46.67 (NCH_2CH=), 47.55 (7-C), 58.33 (3-C), 66.86 (1-C), 123.68 (NCH_2CH=), 124.39 ($CH=CMe_2$), 131.23 ($CH=CMe_2$), 135.62 ($NCH_2CH=C$) (Found: M^+ 275.2614. $C_{19}H_{33}N$ requires *M*, 275.2613); *m*/*z* 275 (57%, M^+), 124 (96), 96 (100), 69 (99, C_5H_9).

2-(Linalyloxy)-1,7,7-trimethyl-2-azabicyclo[2.2.1]heptane 12b

Following the same procedure as for the hydroxylamine **12a**, the amine **3b** (191 mg, 0.69 mmol) and the oxaziridine **11** (220 mg, 0.83 mmol) gave, after purification by flash chromatography, eluting with petrol, the hydroxylamine **12b** (51 mg, 25%) as an oil [65% de by chiral HPLC (column: Waters Symmetry, 150 × 4 mm; eluent: 60–73% MeCN in H_2O containing 0.1% TFA, flow rate: 1 cm^3 min^{-1}; detection by UV at 215 nm)]; R_f 0.7 (petrol); ν_{max}(neat)/cm^{-1} 2940 (C–H); δ_H(400 MHz, $CDCl_3$) 0.87 (3H, s, CH_3), 0.93 (3H, s, CH_3), 0.99 (3H, s, CH_3), 1.20–1.23 (3H, m, CH_3), 1.24–1.29 (1H, m, 5-H_{endo}), 1.30–1.38 (1H, m, 6-H_{endo}), 1.43–1.51 (2H, m, $CH_2CH_2CH=CMe_2$), 1.51–1.56 (1H, m, 4-H), 1.57–1.61 (3H, m, CH_3), 1.65–1.69 (3H, m, $OCCH_3$), 1.69–1.73 (1H, m, 6-H_{exo}), 1.91–2.00 (2H, m, $CH_2CH=CMe_2$), 2.22–2.31 (1H, m, 5-H_{exo}), 2.41 (1H, d, *J* 10, 3-H_{endo}), 3.46 (1H, dt, *J* 10 and 3, 3-H_{exo}), 4.99–5.06 (2H, m, CH_2=CH), 5.06–5.13 (1H, m, $CH=CMe_2$), 5.88–5.98 (1H, m, $CH_2=CH$); δ_C(100 MHz, $CDCl_3$) (major diastereomer first) 14.74 and 14.56 (10-C), 17.9 (9-C), 18.56 (8-C), 20.27 (CH_3), 23.04 and 22.97 ($CH_2\text{-}CH=CMe_2$), 23.20 (CH_3), 25.65 ($OCCH_3$), 26.28 and 26.21 (5-C), 28.09 (6-C), 39.83 and 39.59 ($CMeCH_2CH_2$), 45.19 (4-C), 46.31 (7-C), 63.56 and 63.42 (3-C), 70.45 (1-C), 80.36 ($OCCH_3$), 112.34 and 112.54 ($CH=CH_2$), 125.02 and 125.07 ($CH=CMe_2$), 130.89 ($CH=CMe_2$), 144.36 ($CH=CH_2$) (Found: M^+ 291.2564. $C_{19}H_{33}NO$ requires *M*, 291.2562); *m*/*z* 291 (0.4%, M^+), 155 (72, MH − $C_{10}H_{17}$), 137 (52, $C_{10}H_{17}$), 81 (100), 69 (78, C_5H_9).

Cleavage of 2-(linalyloxy)-1,7,7-trimethyl-2-azabicyclo[2.2.1]-heptane 12b

Freshly activated zinc dust was added to the hydroxylamine **12b** (130 mg, 0.45 mmol) (45% de) in AcOH–H_2O (1:1) (5 cm^3) and the suspension was subjected to ultrasonic irradiation for 16 h. The suspension was filtered and extracted with Et_2O (5 × 5 cm^3). The organic extracts were washed with H_2O (5 cm^3) and brine (3 cm^3) and the residue was purified by flash chromatography, eluting with petrol–EtOAc (4:1), to give linalool[20] **16** (31 mg, 45%) as an oil; $[\alpha]_D^{23}$ −8.2 (*c* 0.8 in $CHCl_3$). The enantiomeric excess was determined by chiral GC [on an HP5890 GC with an HP5970 MSD (detection by EI mass spectrometry) using a CP-cyclodextrin-b-236-M-19 column, 50 m × 0.25 mm at 95 °C with helium (20 psi) as the carrier gas] to be 46% in favour of the (*R*) enantiomer. The aqueous extract was basified with NaOH (4 M) and extracted with Et_2O (5 × 10 cm^3). The resulting ethereal extract was washed with H_2O (5 cm^3) and brine (5 cm^3) and dried (Na_2SO_4). The solvent was removed *in vacuo* to give 2-azabornane[12] **3** (R = H) (27 mg, 0.22

mmol, 45%) as an oil; δ_H(400 MHz, $CDCl_3$) 0.93 (3H, s, CH_3), 0.94 (3H, s, CH_3), 0.99 (3H, s, CH_3), 1.30–1.36 (1H, m, 6-H_{endo}), 1.44–1.51 (1H, m, 5-H_{endo}), 1.72–1.79 (3H, m, 4-H, 5-H_{exo} and 6-H_{exo}), 1.89 (1H, br m, NH), 2.55 (1H, br d, *J* 9, 3-H_{endo}), 3.04 (1H, br d, *J* 9, 3-H_{exo}); δ_C(100 MHz, $CDCl_3$) 15.33 (CH_3), 18.26 (CH_3), 19.56 (CH_3), 27.49 (5-C), 37.65 (6-C), 46.15 (4-C), 50.17 (3-C), 64.15 (7-C), 77.20 (1-C).

2-(But-2-ynyl)-1,7,7-trimethyl-2-azabicyclo[2.2.1]heptan-3-one 10

NaH (60% dispersion in mineral oil, 1.8 g, 45 mmol) was added to the lactam **8** [16] (4.5 g, 30 mmol) in THF (30 cm^3). After 1 h, *O*-mesylbut-2-ynol [prepared from but-2-ynol (2.23 cm^3, 30 mmol), Et_3N (5 cm^3) and mesyl chloride (2.5 cm^3, 33 mmol) in CH_2Cl_2 (25 cm^3) at 0 °C for 1 h] in THF (10 cm^3) was added and the mixture was stirred for 16 h. Saturated NH_4Cl was added and the mixture was extracted with Et_2O (3 × 10 cm^3), washed with H_2O (2 × 10 cm^3) and brine (10 cm^3) and dried (Na_2SO_4). The solvent was removed *in vacuo* and the residue was purified by flash chromatography, eluting with Et_2O–petrol (4:1), to give the lactam **10** (663 mg, 11%) as an oil; R_f 0.39 (Et_2O–petrol, 4:1); $[\alpha]_D^{26}$ +4.0 (*c* 1.0 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 2235 (C≡C), 1695 (C=O); δ_H(400 MHz, $CDCl_3$) 0.84 (3H, s, CH_3), 0.90 (3H, s, CH_3), 1.24 (3H, s, CH_3), 1.44–1.51 (1H, m, 5-H_{endo}), 1.70–1.75 (4H, m, 6-H_{endo} and C≡CCH_3), 1.80–1.86 (1H, m, 6-H_{exo}), 1.87–2.00 (1H, m, 5-H_{exo}), 2.25 (1H, d, *J* 4, 4-H), 3.73 (1H, dq, *J* 18 and 2, NCH^AH^B), 4.04 (1H, dq, *J* 18 and 2, NCH^AH^B); δ_C(100 MHz, $CDCl_3$) 3.35 (≡CCH_3), 11.70 (10-CH_3), 17.93 (CH_3), 18.25 (CH_3), 23.41 (5-C), 27.51 (NCH_2), 33.16 (6-C), 50.02 (7-C), 55.15 (4-C), 70.57 (1-C), 74.30 (C≡*C*Me), 78.39 (*C*≡CMe), 177.07 (C=O) (Found: M^+ 205.1466. $C_{13}H_{19}NO$ requires *M*, 205.1457); *m*/*z* 205 (12%, M^+), 177 (21, M − CO), 162 (28, M − C_3H_7), 67 (47, NC_4H_5), 53 (100, C_4H_5).

(*E*)-2-(But-2-enyl)-1,7,7-trimethyl-2-azabicyclo[2.2.1]heptane 3c

The lactam **10** (300 mg, 1.46 mmol) in THF (10 cm^3) was added to $LiAlH_4$ (445 mg, 12 mmol) in THF (10 cm^3) at 0 °C. After heating at reflux for 24 h, the mixture was quenched with NaOH (4 M). EtOAc (30 cm^3) and Na_2SO_4 were added and the mixture was filtered. The solvent was removed *in vacuo* and dry toluene (10 cm^3) and DIBAL-H (1.5 M in toluene, 2.35 cm^3, 3.52 mmol) were added. The mixture was heated at 60 °C for 16 h and was quenched with NaOH (4 M). The mixture was extracted with EtOAc (4 × 10 cm^3), washed with H_2O (10 cm^3) and brine (5 cm^3) and dried (Na_2SO_4). The solvent was removed *in vacuo* and the residue was purified by flash chromatography, eluting with Et_2O to give the amine **3c** (98 mg, 36%) as an oil (*E*:*Z*, 6:1 by NMR); $[\alpha]_D^{25}$ +86.5 (*c* 0.7 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 2955 (C–H); δ_H(400 MHz, $CDCl_3$) 0.89 (3H, s, CH_3), 0.93 (3H, s, CH_3), 1.05 (3H, s, CH_3), 1.11–1.18 (1H, m, 6-H_{endo}), 1.37–1.46 (1H, m, 5-H_{endo}), 1.61 (1H, t, *J* 4, 4-H), 1.65–1.69 (3H, m, =CHCH_3), 1.68–1.73 (1H, m, 6-H_{exo}), 1.80–1.89 (2H, m, 3-H_{endo} and 5-H_{exo}), 2.79 (1H, dd, *J* 13 and 7, NCH^AH^BCH=), 3.17–3.25 (2H, m, NCH^AH^BCH= and 3-H_{exo}), 5.44–5.52 (1H, m, NCH_2CH=CH), 5.53–5.62 (1H, m, NCH_2CH=C*H*); δ_C(100 MHz, $CDCl_3$) 13.97 (CH_3), 17.78 (CH_3), 18.48 (CH_3), 19.87 (CH_3), 27.99 (5-C), 28.31 (6-C), 45.16 (4-C), 47.74 (7-C), 51.50 (NCH_2CH=), 58.54 (3-C), 67.16 (1-C), 125.63 (NCH_2CH=*C*H), 130.47 (NCH_2CH=CH) (Found: M^+ 193.1835. $C_{13}H_{23}N$ requires *M*, 193.1831); *m*/*z* 193 (8%, M^+), 91 (99), 69 (51, NC_4H_7), 55 (100, C_4H_7).

2-(But-3-en-2-yloxy)-1,7,7-trimethyl-2-azabicyclo[2.2.1]heptane 12c

Following the same procedure as for the hydroxylamine **12a**, the amine **3c** (62 mg, 0.35 mmol) and the oxaziridine **11** (125 mg, 0.48 mmol) gave, after purification by flash chromatography, eluting with petrol–Et_2O (9:1), the hydroxylamine **12c** (13 mg, 19%) as an oil [67% de by NMR and by chiral HPLC (column: Spherisorb CN, 250 × 4 mm; eluent: 68% MeCN in H_2O containing 0.1% TFA, flow rate: 1 cm^3 min^{-1}; detection by UV at 195 nm)]; R_f 0.8 (petrol); ν_{max}(neat)/cm^{-1} 2965 (C–H); δ_H(400 MHz, $CDCl_3$) 0.86–0.88 (3H, m, CH_3), 0.97–1.02 (6H, m, 2 × CH_3), 1.17 and 1.21 (3H, d, *J* 6, CHCH_3), 1.28–1.37 (2H, m, 5-H_{endo} and 6-H_{endo}), 1.52–1.71 (2H, m, 4-H and 5-H_{exo}), 2.27 (1H, br s, 6-H_{exo}), 2.42 (1H, br s, 3-H_{endo}), 3.50 (1H, br s, 3-H_{exo}), 4.01–4.11 (1H, m, OC*H*CH_3), 5.01–5.06 (1H, m, CH=CH^AH^B), 5.10–5.18 (1H, m, CH=CH^AH^B), 5.81–5.90 (1H, m, C*H*=CH_2); δ_C(100 MHz, $CDCl_3$) (major diastereomer only) 13.93 (CH_3), 18.62 (CH_3), 19.41 (CH_3), 20.20 (CH_3), 27.84 (5-C), 29.68 (6-C), 45.21 (4-C), 46.38 (7-C), 61.49 (3-C), 70.69 (1-C), 79.98 (O*C*HCH_3), 114.36 (CH=*C*H_2), 141.86 (*C*H=CH_2); *m*/*z* 209 (1%, M^+), 71 (67, OC_4H_7), 55 (100, C_4H_7).

(*Z*)-2-(But-2-enyl)-1,7,7-trimethyl-2-azabicyclo[2.2.1]heptan-3-one 9d

The lactam **10** (321 mg, 1.56 mmol) in hexane (15 cm^3) and Lindlar's palladium catalyst was stirred under hydrogen for 30 min at 0 °C. The mixture was filtered and the solvent was removed *in vacuo*. The residue was purified by flash chromatography, eluting with Et_2O–petrol (3:1), to give the lactam **9d** (255 mg, 1.23 mmol, 79%) as an oil (*Z*:*E*, 6:1 by NMR); R_f 0.14 (petrol–Et_2O, 1:1), $[\alpha]_D^{23}$ +8.8 (*c* 1.1 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 1690 (C=O); δ_H(400 MHz, $CDCl_3$) 0.85 (3H, s, CH_3), 0.94 (3H, s, CH_3), 1.15 (3H, s, CH_3), 1.44–1.51 (1H, m, 6-H_{endo}), 1.55–1.63 (1H, m, 5-H_{endo}), 1.68 (3H, dd, *J* 7 and 1, =CHCH_3), 1.71–1.79 (1H, m, 6-H_{exo}), 1.89–1.97 (1H, m, 5-H_{exo}), 2.28 (1H, d, *J* 4, 4-H), 3.80–3.85 (2H, m, NCH_2CH=), 5.30–5.37 (1H, m, NCH_2CH=CH), 5.47–5.55 (1H, m, NCH_2CH=C*H*); δ_C(100 MHz, $CDCl_3$) 12.13 (CH_3), 12.86 (CH_3), 18.07 (CH_3), 18.45 (CH_3), 23.50 (5-C), 33.73 (6-C), 35.18 (N*C*H_2CH=), 49.88 (7-C), 55.13 (4-C), 70.51 (1-C), 126.14 (NCH_2CH=*C*H), 126.69 (NCH_2CH=CH), 177.60 (C=O) (Found: M^+ 207.1620. $C_{13}H_{21}NO$ requires *M*, 207.1623); *m*/*z* 207 (38%, M^+), 179 (46, M − CO), 164 (82), 69 (48, NC_4H_7), 55 (100, C_4H_7).

(*Z*)-(2)-(But-2-enyl)-1,7,7-trimethyl-2-azabicyclo[2.2.1]heptane 3d

The lactam **9d** (254 mg, 1.23 mmol) in THF (15 cm^3) was added to $LiAlH_4$ (233 mg, 6.1 mmol) in THF (25 cm^3) at 0 °C. The mixture was heated under reflux for 24 h and was quenched with NaOH (4 M). EtOAc (30 cm^3) and Na_2SO_4 were added and the mixture was filtered. The solvent was removed *in vacuo* and the residue was purified by flash chromatography, eluting with Et_2O, to give the amine **3d** (138 mg, 58%) as an oil (*E*:*Z*, 6:1 by NMR); $[\alpha]_D^{25}$ +82.7 (*c* 1.1 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 2955 (C–H); δ_H(400 MHz, $CDCl_3$) 0.91 (3H, s, CH_3), 0.94 (3H, s, CH_3), 1.04 (3H, s, CH_3), 1.10–1.20 (1H, m, 6-H_{endo}), 1.38–1.48 (1H, m, 5-H_{endo}), 1.60 (1H, t, *J* 4, 4-H), 1.66 (3H, d, *J* 5, =CHCH_3), 1.67–1.73 (1H, m, 5-H_{exo}), 1.81–1.93 (2H, m, 3-H_{endo} and 6-H_{exo}), 3.01–3.07 (1H, m, NCH^AH^B), 3.10–3.17 (1H, m, NCH^AH^B), 3.22–3.28 (1H, m, 3-H_{exo}), 5.43–5.51 (2H, m, NCH_2CH=C*H*); δ_C(100 MHz, $CDCl_3$) 13.14 (CH_3), 14.06 (CH_3), 18.45 (CH_3), 19.86 (CH_3), 27.78 (5-C), 28.51 (6-C), 45.16 (4-C), 45.53 (NCH_2CH=), 47.53 (7-C), 58.42 (3-C), 66.94 (1-C), 124.39 (NCH_2CH=*C*H), 129.83 (NCH_2CH=CH) (Found: M^+ 193.1828. $C_{13}H_{23}N$ requires *M*, 193.1831); *m*/*z* 193 (25%, M^+), 178 (32, M − CH_3), 149 (100).

2-(But-3-en-2-yloxy)-1,7,7-trimethyl-2-azabicyclo[2.2.1]heptane 12d

Following the same procedure as for the hydroxylamine **12a**, the amine **3d** (59 mg, 0.28 mmol) and the oxaziridine **11** (110 mg, 0.4 mmol) gave, after purification by flash chromatography, eluting with petrol–Et_2O (9:1), the hydroxylamine **12d** (12 mg, 19%) as an oil (36% de by NMR); spectroscopic data as for **12c**.

2-Benzyl-1,7,7-trimethyl-2-azabicyclo[2.2.1]heptane 13

NaH (60% dispersion in mineral oil, 655 mg, 16 mmol) was added to the lactam **8** (500 mg, 3.27 mmol) in THF (30 cm^3). After 1 h, benzyl bromide (0.77 cm^3, 6.5 mmol) was added. After a further 16 h, the mixture was quenched with saturated aqueous NH_4Cl. The mixture was extracted with Et_2O (3 × 10 cm^3), washed with H_2O (2 × 10 cm^3) and brine (10 cm^3) and dried (Na_2SO_4). The solvent was removed *in vacuo* and the residue was purified by flash chromatography, eluting with petrol–Et_2O (1 : 1), to give the lactam (precursor to the amine **13**) (700 mg, 88%) as needles; R_f 0.19 (1 : 1, petrol–Et_2O); mp 79–81 °C; $[\alpha]_D^{24}$ +10.6 (*c* 1.0 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 1680 (C=O); δ_H(400 MHz, $CDCl_3$) 0.84 (3H, s, CH_3), 0.95 (3H, s, CH_3), 1.06 (3H, s, CH_3), 1.34–1.41 (1H, m, 6-H_{endo}), 1.46–1.54 (1H, m, 5-H_{endo}), 1.61–1.69 (1H, m, 6-H_{exo}), 1.90–1.99 (1H, m, 5-H_{exo}), 2.36 (1H, d, *J* 4, 4-H), 4.30 (1H, d, *J* 15, NCH^AH^BPh), 4.36 (1H, d, *J* 15, NCH^AH^BPh), 7.20–7.30 (5H, m, Ar*H*); δ_C(100 MHz, $CDCl_3$) 12.43 (CH_3), 18.07 (CH_3), 18.49 (CH_3), 23.56 (5-C), 33.26 (6-C), 42.47 (NCH_2Ph) 49.76 (7-C), 55.14 (4-C), 71.14 (1-C), 127.09 (Ar*C*H), 128.06 (Ar*C*H), 128.43 (Ar*C*H), 138.98 (Ar*C*), 178.39 (C=O) (Found: M^+ 243.1621. $C_{16}H_{21}NO$ requires *M*, 243.1623); *m*/*z* 243 (47%, M^+), 228 (7, M − CH_3), 215 (39, M − CO), 91 (100, $PhCH_2$) (Found: C, 78.88; H, 8.73; N, 5.87. $C_{16}H_{21}NO$ requires C, 78.97; H, 8.70; N, 5.76%).

This lactam (617 mg, 2.53 mmol) in THF (20 cm^3) was added to $LiAlH_4$ (482 mg, 12.5 mmol) in THF (25 cm^3) at 0 °C. After heating under reflux for 16 h, the mixture was quenched with NaOH (4 M). EtOAc (30 cm^3) and Na_2SO_4 were added and the mixture was filtered. The solvent was removed *in vacuo* and the residue was purified by flash chromatography, eluting with petrol–EtOAc (2 : 1), to give the amine **13** (481 mg, 83%) as an oil; R_f 0.95 (1 : 1, petrol–EtOAc); $[\alpha]_D^{24}$ +93.6 (*c* 1.1 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 2955 (C–H); δ_H(400 MHz, $CDCl_3$) 0.98 (3H, s, CH_3), 1.03 (3H, s, CH_3), 1.15 (3H, s, CH_3), 1.20–1.30 (1H, m, 6-H_{endo}), 1.53–1.60 (1H, m, 5-H_{endo}), 1.67 (1H, t, *J* 4, 4-H), 1.73–1.81 (1H, m, 6-H_{exo}), 1.83 (1H, d, *J* 9, 3-H_{endo}), 1.93–2.00 (1H, m, 5-H_{exo}), 3.19 (1H, dt, *J* 9 and 4, 3-H_{exo}), 3.39 (1H, d, *J* 14, NCH^AH^BPh), 3.95 (1H, d, *J* 14, NCH^AH^BPh), 7.22–7.24 (1H, m, Ar*H*), 7.29–7.39 (4H, m, Ar*H*); δ_C(100 MHz, $CDCl_3$) 14.08 (CH_3), 18.51 (CH_3), 19.86 (CH_3), 28.50 (5-C), 28.52 (6-C), 45.45 (4-C), 47.66 (7-C), 53.38 (NCH_2Ph), 58.77 (3-C), 67.01 (1-C), 126.25 (Ar*C*H), 127.99 (Ar*C*H), 128.05 (Ar*C*H), 141.68 (Ar*C*CH_2N) (Found: M^+ 229.1832. $C_{16}H_{23}N$ requires *M*, 229.1831); *m*/*z* 229 (36%, M^+), 214 (34, M − CH_3), 138 (10, M − CH_2Ph), 91 (100, CH_2Ph).

2-Benzyl-1,7,7-trimethyl-2-azabicyclo[2.2.1]heptane 2-oxide 14

MCPBA (80%, 47 mg, 0.22 mmol) was added to the amine **13** (50 mg, 0.22 mmol) in $CDCl_3$ (1 cm^3). The mixture was stirred for 10 min and the product *N*-oxide **14** (complexed to *m*-chlorobenzoic acid, 6 : 1 mixture of diastereomers by NMR) was characterised by NMR: (major diastereomer) δ_H(400 MHz, $CDCl_3$) 0.88 (3H, s, 10-CH_3), 0.97 (3H, s, 9-CH_3), 1.41 (3H, s, 8-CH_3), 1.47–1.55 (1H, m, 5-H_{endo}), 1.83–1.92 (1H, m, 6-H_{exo}), 1.97–2.06 (1H, m, 5-H_{exo}), 2.18 (1H, d, *J* 4, 4-H), 2.29–2.37 (1H, m, 6-H_{endo}), 3.80 (1H, d, *J* 13, 3-H_{endo}), 4.59 (1H, d, *J* 13, NCH^AH^BPh), 4.65 (1H, dt, *J* 13 and 4, 3-H_{exo}), 5.45 (1H, d, *J* 13, NCH^AH^BPh), 7.26–7.40 (5H, m, Ar*H*), 7.66–7.70 (2H, m, Ar*H*), 7.95 (1H, dt, *J* 8 and 1, Ar*H*), 8.06 (1H, t, *J* 2, Ar*H*); δ_C(100 MHz, $CDCl_3$) 10.98 (10-C), 20.93 (8-C), 22.34 (9-C), 25.19 (5-C), 29.84 (6-C), 43.99 (4-C), 50.87 (7-C), 68.94 (3-C), 77.58 (NCH_2Ph), 88.59 (1-C), 127.79 (Ar*C*H), 128.36 (Ar*C*H), 128.72 (Ar*C*H), 129.13 (Ar*C*H), 129.61 (Ar*C*H), 129.82 (Ar*C*H), 130.05 (Ar*C*H), 130.96 (Ar*C*H), 132.45 (Ar*C*CO_2H), 132.80 (Ar*C*H), 133.82 (ArCCl), 137.12 (Ar*C*CH_2N), 170.00 (CO_2H). The results of NOE experiments indicated that the major diastereomer had the *N*-benzyl group in the *endo* position, since irradiation of NCH^AH^B caused an enhancement (7.6%) of 6-H_{endo} and irradiation of *N*CH_2-*o*-C_6H_2 caused an enhancement (9.4%) of 6-H_{endo}.

Cope elimination of 2-benzyl-1,7,7-trimethyl-2-azabicyclo[2.2.1]-heptane 2-oxide 14

MCPBA (80%, 92 mg, 0.44 mmol) was added to the amine **13** (100 mg, 0.44 mmol) in CH_2Cl_2 (4 cm^3). After 10 min, the mixture was washed with aqueous K_2CO_3 (2 × 5 cm^3), H_2O (5 cm^3) and brine (5 cm^3) and dried (Na_2SO_4). The CH_2Cl_2 solution was allowed to stand for 24 h, the solvent was removed *in vacuo*, and the residue was purified by flash chromatography, eluting with petrol–Et_2O (1 : 1), to give the hydroxylamine **15** (83 mg, 78%) as an oil; $[\alpha]_D^{24}$ +20.6 (*c* 0.97 in $CHCl_3$); ν_{max}($CDCl_3$)/cm^{-1} 3235 (O–H), 1650 (C=C); δ_H(400 MHz, $CDCl_3$) 0.81 (3H, s, CH_3), 1.13 (3H, s, CH_3), 1.33–1.41 (1H, m, C$H^AH^BCH_2$C=CH_2), 1.88–1.99 (2H, m, C$H^AH^B$$CH_2$C=$CH_2$ and NCH_2C*H*), 2.24–2.33 (1H, m, CH^AH^BC=CH_2), 2.38–2.46 (1H, m, CH^AH^BC=CH_2), 2.54–2.60 (1H, m, NCH^AH^BCH), 2.77 (1H, dd, *J* 12 and 4, NCH^AH^BCH), 3.71 (1H, d, *J* 13, NCH^AH^BPh), 3.79 (1H, d, *J* 13, NCH^AH^BPh), 4.74–4.78 (2H, m, C=CH_2), 7.30–7.33 (5H, m, Ar*H*); δ_C(100 MHz, $CDCl_3$) 23.35 (CH_3), 27.12 (CH_3), 27.89 (*C*$H_2$$CH_2$C=$CH_2$), 30.62 (*C*$H_2$C=$CH_2$), 43.60 (*C*$Me_2$), 47.32 (N$CH_2$*C*H), 61.08 (N*C*$H_2$CH), 65.37 (N*C*$H_2$Ph), 102.96 (C=*C*$H_2$), 127.34 (Ar*C*H), 128.29 (Ar*C*H), 129.59 (Ar*C*H), 137.47 (Ar*C*), 162.28 (*C*=CH_2) (Found: M^+ 245.1774. $C_{16}H_{23}NO$ requires *M*, 245.1780); *m*/*z* 245 (7%, M^+), 136 (16, M − C_8H_{13}), 91 (76, $PhCH_2$), 84 (100).

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References

1 J. Meisenheimer, *Chem. Ber.*, 1919, **52**, 1667.
2 A. C. Cope and R. F. Kleinschmidt, *J. Am. Chem. Soc.*, 1944, **66**, 1929; A. C. Cope and P. H. Towle, *J. Am. Chem. Soc.*, 1949, **71**, 3423.
3 V. Rautenstrauch, *Helv. Chim. Acta*, 1973, **56**, 2492.
4 M. Moriwaki, Y. Yamamoto, J. Oda and Y. Inouye, *J. Org. Chem.*, 1976, **41**, 303.
5 M. T. Reetz and E. H. Lauterbach, *Tetrahedron Lett.*, 1991, **32**, 4481.
6 S. G. Davies and G. D. Smyth, *Tetrahedron: Asymmetry*, 1996, **7**, 1001 and 1005.
7 D. Enders and H. Kempen, *Synlett*, 1994, 969.
8 M. Moriwaki, Y. Yamamoto, J. Oda and Y. Inouye, *J. Org. Chem.*, 1976, **41**, 300.
9 J. E. H. Buston, I. Coldham and K. R. Mulholland, *Tetrahedron: Asymmetry*, 1998, **9**, 1995.
10 J. E. H. Buston, I. Coldham and K. R. Mulholland, *Synlett*, 1997, 322.
11 C. M. Cain, R. P. C. Cousins, G. Coumbarides and N. S. Simpkins, *Tetrahedron*, 1990, **46**, 523.
12 P. G. Gassman and K. Shudo, *J. Am. Chem. Soc.*, 1971, **93**, 5899.
13 S. Oae and H. Togo, *Synthesis*, 1981, 371.
14 B. E. Love and J. Ren, *J. Org. Chem.*, 1993, **58**, 5556.
15 A related isomer of amine **1**, R = H has been prepared subsequently by S. M. Starling, S. C. Vonwiller and J. N. H. Reek, *J. Org. Chem.*, 1998, **63**, 2262.
16 R. K. Boeckman, S. G. Nelson and M. D. Gaul, *J. Am. Chem. Soc.*, 1992, **114**, 2258.
17 F. A. Davis, *Org. Synth.*, 1988, **66**, 203.
18 A. C. Cope and E. R. Trumbull, *Org. React.*, 1960, **11**, 317.
19 D. A. Forsyth, W. Zhang and J. A. Hanley, *J. Org. Chem.*, 1996, **61**, 1284.
20 G. Ohloff and E. Klein, *Tetrahedron*, 1962, **18**, 37.

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